Remarks/Arguments:

Interview Summary

The undersigned wishes to thank Examiner Maier for the courtesy shown the undersigned during a telephone interview held February 2, 2004.

During the interview we discussed in detail the rejection based on 35 U.S.C § 112, in particular, indefiniteness allegedly resulting from use of the phrase "based on glucosamine sulfate as the glucosamine material." As discussed in the telephone interview, reference to glucosamine sulfate in the material in quotes refers to glucosamine sulfate as the basis for calculating the ratio, not as a limitation on the scope of the term "glucosamine material". As also indicated during the interview, the reference to glucosamine sulfate as the basis for calculation of the ratio resulted from the fact that glucosamine sulfate was the basis on which the examples were conducted and on which data from the examples were reported. However, it was also pointed out that the application also contains an approximate correlation of the corresponding glucosamine (base):analgesic compound weight ratio. The Examiner stated she would have preferred to see a molar ratio rather than a weight ratio. The undersigned pointed out that, although not used in the examples, that ratio could also be calculated from the disclosure as well. It was agreed that a clarification of the manner in which the ratio was calculated would be presented for further consideration by the Examiner. That clarification has now been set forth in claims 1 and 16.

The rejections of several claims as anticipated by or obvious over Giorgetti and/or as obvious over Paradies were discussed and confirmed to be based on the indefiniteness rejection discussed above, such that withdrawal was dependent on an adequate clarification of that indefiniteness rejection.

During the interview, the Examiner also expressed that, following a review of the art cited in the application, she had reservations and/or concerns over some cited but unapplied art. Mentioned in particular was Meisner, U.S. Patent 4,647,483, in particular data set forth in example 8 of that patent.

The comments and concerns of Examiner as expressed in the telephone interview were extremely helpful in clarifying the remaining issues. While no specific agreement was reached, the following amendments have been made to address and obviate each of the issues raised by the Examiner. It is hoped this effort will facilitate reconsider and allowance of all

claims without the necessity for filing of an appeal, a request for continued examination or filing of a continuing application.

Claims 1, 11-12, and 14-16 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

This ground of rejection is based on the examiner's assertion that it is unclear if the language "based on glucosamine sulfate as the glucosamine material," as used in claims 1 and 16, is used to limit those claims to glucosamine sulfate or if that language is merely being used as the basis for calculation of the weight ratio (glucosamine material : analgesic compound) without otherwise limiting the scope of those claims.

In response, Applicants respectfully submit that claims 1 and 16 have now been amended to clarify that the reference to glucosamine sulfate in connection with the glucosamine material : analgesic compound ratio is simply a method for calculating the ratio and is not a limitation of the claims to glucosamine sulfate. As indicated in the telephone interview, glucosamine material used and reported in the examples was glucosamine sulfate and accordingly is also carried forward into the claims. Thus, the ratio as defined is consistent with the data reported in the application. Further, this intention is clearly expressed by the disclosure at page 4, lines 24 -29 of the specification:

> "In compositions of the present invention, the glucosamine material may be one or more of the following: the α- or ß-form of glucosamine or mixtures thereof, N-acetylglucosamine, or various pharmaceutically acceptable salts of any of them, in particular glucosamine sulfate or glucosamine HCl."

This limitation has been incorporated into claim 1 for clarity.

Accordingly, in accordance with the foregoing, we submit that reference to the term "glucosamine sulfate" in connection with the claimed weight ratio is intended to operate only as a limitation on the method of calculation of the ratio and not on the selection of any particular glucosamine material.

Withdrawal of this rejection is respectfully requested.

Claim 1 was again rejected under 35 U.S.C. 102 (e) as being anticipated by Giorgetti (B).

Insofar as the undersigned can determine, and as confirmed during the telephone interview, this continuing rejection is based solely on the above identified indefiniteness rejection relating to the use of the term "glucosamine sulfate" in connection with the ratio set forth in claim 1. The Office Action states that the Examiner had considered the argument set forth in the October 6, 2003 response, but found that argument to be unpersuasive. Applicant respectfully disagrees.

As indicated in the October, 2003, amendment, Giorgetti teaches, for example in Example 14, compositions comprising "Ketoprofen glucosamine salt, 1.7 g, equivalent to Ketoprofen acid, 1 g." Based on those numbers, it is clear that the weight ratio of glucosamine to ketoprofen is 0.7:1. That is also true for the composition of Example 31 except that the ratio is 17g of glucosamine salt which is the equivalent of 10g (i.e., 10% by weight) ketoprofen acid. Thus the weight ratio is once again 0.7:1.

By contrast the application, as now (and as previously) claimed requires a glucosamine sulfate : analgesic compound weight ratio substantially above that taught by Giorgetti. That is, Giorgetti sets forth a glucosamine (base) : ketoprofen ratio of 0.7:1. That ratio is equivalent to a glucosamine (sulfate) : ketoprofen ratio of about 1.2:1, whereas applicants synergistic combination of glucosamine material and ketoprofen requires a weight ratio of glucosamine (sulfate) : ketoprofen of 2:1 or greater, approximately 40% higher than the ratio disclosed in Giorgetti. Clearly the ratio taught by Giorgetti is well below that required to produce synergistic relief of acute pain when administered orally, as shown and claimed in the present application.

For the reasons set forth above, applicants' claims as amended now clearly distinguish over the teaching of Giorgetti. Accordingly withdrawal of the rejection is respectfully requested.

Claims 1, 14, and 15 again stand rejected under 35 U.S.C. 103(a) as being unpatentable over Paradies (AH).

In the Office Action, Examiner states that Applicants' argument of October 6, was considered but found not to be persuasive.

Again, this rejection appears to be based solely on the indefiniteness rejection discussed in detail above. The amendment and clarification set forth with respect to the glucosamine : analgesic ratio above is believed to obviate this ground for rejection. Applicants respectfully submit that Paradies does not teach or suggest ratios which produce synergistic relief of acute pain when taken orally.

Paradies teaches in column 1, lines 20 and following, that the problem addressed "is solved ...by hydrogen-bridge bound complexes having a stoichiometry of 1:1...." between certain alkanoic acids and amino sugars. Among the amino sugars, glucosamine, although not exemplified, is listed at column 2, line 32. This reference, however, only teaches a stoichiometry of 1:1, i.e., that equimolar amounts of the acid and the amino sugar must be utilized. Thus, in example 1 equimolar amounts of ibuprofen and the amino sugar were utilized, and the weight ratio of amino sugar to analgesic was 0.724:1 (i.e., 181:250). Likewise in example 2, equimolar amounts were used, such that the weight ratio of amino sugar:ibuprofen was 0.95:1 (i.e., 195.2:206.3). There is no specific teaching as to the use of glucosamine compositions.

Paradies does not teach or suggest a weight ratio of 2:1 or greater or teach or suggest in any that modification of the 1:1 ratio would produce synergistic analgesic efficacy for treatment of acute pain when administered orally.

In view of the foregoing, applicants claims as currently amended clearly distinguish over the teaching of Paradies. Accordingly withdrawal of this rejection is respectfully requested.

Claims 1-6, 11-12 and 14-16 were again rejected under 35 U.S.C. 103(a) as being unpatentable over Petrus (A) in view of either Giorgetti (B) or Paradies (AH).

The Office Action correctly alleged that Petrus teaches a topical ointment formulation comprising 4:1 weight ratio of glucosamine sulfate to ibuprofen together with a penetration enhancer, for treatment of musculoskeletal disorders. It was examiner's position that "one of ordinary skill in the art would reasonably expect success in reformulating the weight ratios taught by Petrus into an oral dosage form with a reasonable expectation of success." Presumably this expectation arises in spite of Petrus' teaching away from an oral dosage form, and in spite of the teaching by both Giorgetti and Paradies of an oral dosage form which is limited to equimolar proportions of glucosamine or a glucosamine-like anti-

inflammatory compound and an analgesic compound such as Ibuprofen or ketoprofen. We submit that those disclosures do not combine to teach or suggest the claimed synergistic combination for treatment of acute pain. Petrus itself, it teaches against the use of oral dosage forms for the reasons previously cited. If our understanding is correct, examiner's reliance on Giorgetti and Paradies is only for the purpose of showing that it is known to combine an amine such as glucosamine and either Ketoprofen or Ibuprofen into an oral dosage form.

Obviousness of combining the cited references and/or obviouness from Petrus alone is dependent on whether or not the references alone or together provide a reasonable expectation of success, as examiner has rightly noted in the quote above. Applicants submit that, while these references can be arguably combined to enable one of ordinary skill in the art to formulate an oral dosage form utilizing the ratio taught by Petrus, there is nothing in Petrus or in any of the other cited references which would teach or suggest a synergistic oral composition or method of treatment of acute pain. The claims require that "the weight ratio of glucosamine material to analgesic compound is such that the analgesic efficacy of the oral dosage form in alleviating the symptoms of acute pain when administered orally is greater than the analgesic efficacy of the analgesic compound alone at the dosage level for the analgesic compound." There is nothing in any of the cited references or combination of references which would teach or suggest this limitation of applicants' claims.

Stated otherwise, one of ordinary skill in the art following the examiner's suggestion would expect to obtain a composition or method for treatment in which the effect of combining glucosamine with an analgesic compound would be either additive or sub-additive. Because synergism is inherently unpredictable, one skilled in the art could not reasonably expect to obtain a synergistic composition or method as claimed from the teaching of Petrus, Petrus in combination with Giorgetti, Petrus in combination with Paradies, or any other combination of these references. Thus, the dosage form and/or method of treatment evidencing that synergy is unexpected, unobvious and patentable over the art of record.

For the foregoing reasons, withdrawal of these grounds for rejection is respectfully requested.

Claims 1, 2, 12, 14, and 15, were rejected under 35 U.S.C. 103(a) as being unpatentable over Giorgetti (B).

This ground for rejection is respectfully traversed for the same reasons as those set forth in the above response to the §102(e) rejection based on Giorgetti. Since that rejection was predicated on the rejection for indefiniteness, it is believed that clarification of the basis for calculation of the ratio has likewise obviated this ground for rejection. Accordingly, withdrawal is respectfully requested.

Meisner, U.S. Patent 4,647,453

While this reference has not been applied in writing by the examiner, it was called to the attention of the undersigned during the above identified telephone conference. In particular, Example 8 of Meisner was noted by the examiner. Applicants' comments on this references are summarized below.

The example to which we were directed describes a 66 year old woman with osteoarthritis. She was treated with a daily regimen that included three 600 mg Nalfon tablets or capsules and 1000 mg of glucosamine. She was reported to have improved and become pain free after six months of this treatment.

Meisner's disclosure and claims refer to inflammation and its treatment in which pain is secondary to the inflammatory process. It took a period of 6 months after the start of treatment for the pain to subside. This fact pattern alone strongly suggests the need for more effective control to immediately and quickly alleviate pain while the anti-inflammatory ingredients do their job and cause a longer term reduction of pain as a result of tissue repair and reduction in inflammation.

Meisner does not disclose or suggest a formulation, dosage form or dosage regimen that would provide super-additive analgesia as required by the claims of the present application, which specifics a glucosamine material to analgesic compound weight ratio of about 2:1 or greater. Based on the disclosure set forth in Example 8 of Meisner, the applicable weight ratio of the daily dose was 1000 : 1800, in which the 1000 represents the weight of glucosamine administered daily, and in which the 1800 represents three tablets each of which contain 600 mg of fenoprofen. There is no suggestion or requirement that any of these be taken in any particular order or in any particular ratio. However, the daily dose does recite administration of these medications in a weight ratio of 1000 to 1800, which corresponds to a glucosamine to fenoprofen weight ratio of 0.55 :1 assuming the glucosamine was administered as the free base. However, it is more likely that the glucosamine was administered as the

sulfate. The amount of glucosamine sulfate corresponding to 1000 mg of glucosamine base would be (1000 x 277)/ 179 = 1547 mg; thus the weight ratio based on glucosamine sulfate to fenoprofen was 0.86 :1, which was clearly below the threshold required for synergistic activity (approximately 2:1 or above) as disclosed and claimed the present application.

In view of the foregoing, it is clear that Meisner neither teaches nor suggests the synergistic composition or method claimed in the present application.

In view of the examiner's stated intention to cite the Meisner reference, and in view of the foregoing analysis of that reference, applicants request that the finality of the rejection be withdrawn to permit entry and citation of Meisner as a new ground for rejection presented by examiner, and so that applicants remarks concerning the Meisner may be made of record and considered.

In view of the foregoing amendments and remarks, the present invention is believed to distinguish over the art of record and to be in condition for allowance. Accordingly, an early notification to that effect is respectfully requested. In the event that there are still outstanding issues which may be resolved by interview, applicants respectfully request that the examiner contact the undersigned at her convenience by telephone to discuss such issues.

Respectfully submitted,

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Dated: March 23, 2004

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